Heliyon 9 (2023) e20407

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Recent advances in glucose oxidase-based nanocarriers for tumor targeting therapy

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ARTICLE INFO

Keywords:
Glucose oxidase
Nanocarriers
Targeted therapy
Cancer

ABSTRACT

Glucose oxidase (GOx) can specifically catalyze the conversion of β-D-glucose into gluconic acid and hydrogen peroxide (H_2O_2) in the presence of oxygen, making it promising for tumor starvation therapy and oxidative therapy. However, GOx's immunogenicity, poor in vivo stability, short half-life, and potential systemic toxicity, limit its application in cancer therapy. Nanocarriers are capable of improving the pharmacological properties of therapeutic drugs (e.g. stability, circulating half-life, and tumor accumulation) and lower toxicity, hence resolving GOx issues and enhancing its efficacy. Although the application of targeted nanocarriers based on GOx has recently flourished, this field has not yet been reviewed and evaluated. Herein, we initially examined the mechanism of GOx-based nanocarriers for enhanced tumor therapy. Also, we present a comprehensive and up-to-date review that highlights GOx-based nanocarriers for tumor targeting therapy. This review expands on GOx-based nano-targeted combination therapies from both passive and active targeting perspectives, meanwhile, active targeting is further classified into ligand-mediated targeting and physical-mediated targeting. Furthermore, this review also emphasizes the present challenges and promising advancements.

1. Introduction

Cancer is a major cause of death in 2022, with an estimated 19.3 million new cases and 10 million deaths [1]. Since chemotherapy drugs have a non-selective effect on normal cells, most patients receiving conventional chemotherapy have side effects. Enzymatic therapy, a novel oncology strategy, destroys tumor growth by depleting vital nutrients [2], degrading tumor extracellular matrix [3] of tumors, or activating prodrugs [4]. Enzymes have unique advantages over conventional chemotherapeutic drugs [5], such as high

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https://doi.org/10.1016/j.heliyon.2023.e20407
Received 16 July 2023; Received in revised form 21 September 2023; Accepted 22 September 2023
Available online 25 September 2023

biodegradability and catalytic efficiency. So far, asparaginase [6] and PEGylated arginine deiminase [7] have been approved by the United States Food and Drug Administration (FDA) as two antitumor enzymes. A promising natural enzyme is glucose oxidase (GOx) for cancer starvation therapy and oxidative therapy, which catalyzes the oxidation of β-D-glucose to hydrogen peroxide (H_2O_2) and gluconic acid [8]. GOx can effectively cut off the energy supply to tumor cells by depleting intra-tumoral glucose, consequently hindering tumor growth [9]. However, the usage of GOx is currently restricted due to its immunogenicity, low in vivo stability, short half-life, and probable systemic toxicity.

The use of nanomaterials in cancer therapy is gaining popularity due to their distinguishing features such as better pharmacological properties of medicinal compounds (e.g. stability, circulating half-life, and tumor accumulation) and efficacy [10]. With the aid of the enhanced permeation and retention (EPR) effect [11], nanocarriers can escape via the leaky endothelium and become stuck inside the tumor due to a flawed lymphatic drainage system, which can increase nanomaterial aggregation in solid tumor tissue. The EPR effect enables nanocarriers to be passively targeted to solid tumors. In contrast to passive targeting, active targeting of solid tumors can deliver a higher concentration of drugs to the target area with fewer adverse effects [12]. In recent years, GOx-based nanoparticle delivery systems for tumor targeting therapy have developed rapidly, and there have been several reviews of GOx-related tumor therapeutics and diagnostics [9,13–17], but tumor-targeted therapies involving GOx-based therapies have still not been analyzed and summarized. In this review, we discuss the mechanism of GOx-based nanocarriers for enhanced tumor therapy. Moreover, we also lay emphasis on its passive and active targeting-based tumor therapy in order to promote the development of targeting of tumor therapy and nanomaterials. Finally, we discuss the current challenges to clinical translation as well as its promising future development.

2. Mechanism of GOx-based nanocarriers for treating tumors

Glucose is a key component that contributes to tumor growth by providing energy [18]. GOx could transform glucose to gluconic acid and H_2O_2, providing an alternative method for cancer starvation therapy [19]. Furthermore, at large concentrations, H_2O_2 could trigger cytotoxic effects via H_2O_2-dependent acceleration of tumor cell apoptosis [20]. As a consequence, introducing GOx into the tumor is anticipated to consume intra-tumoral glucose while simultaneously boosting the H_2O_2 level to kill cancer cells. Based on these two properties, GOx has been used to treat cancer by starvation therapy and oxidative therapy. To understand the mechanism of action of GOx-based *nanocarriers* in tumor therapy, we will begin with starvation therapy and then go to oxidative therapy in the sections that

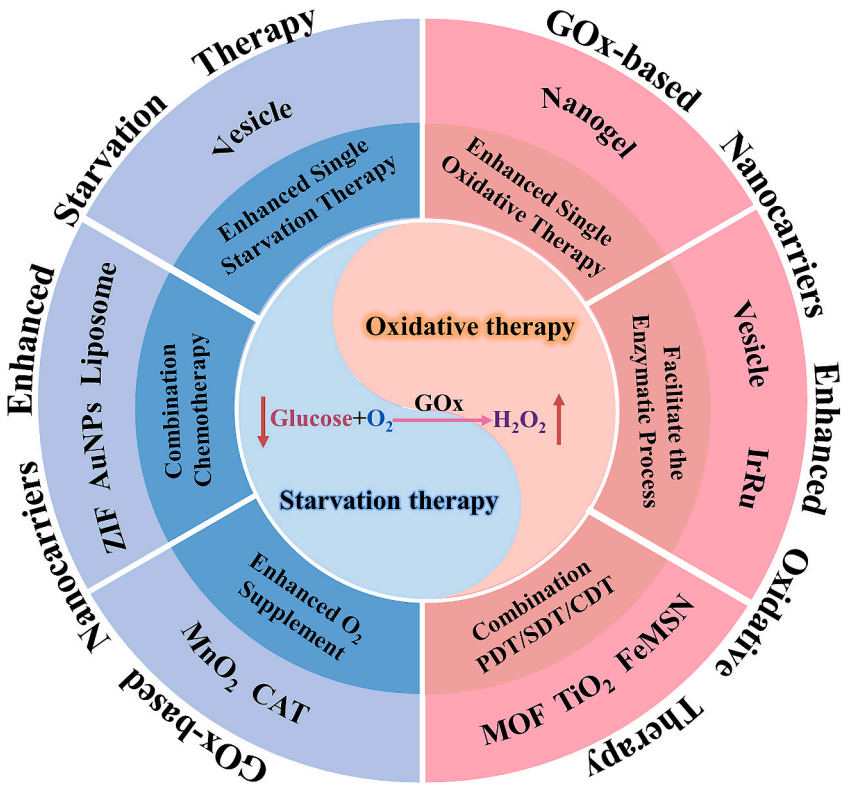

Fig. 1. Mechanism of GOx-based Nanocarriers Enhanced Tumor Therapy
Notes: Starvation and oxidative therapies are common categories for GOx-based nanoparticle drug delivery systems for enhanced tumor therapy. Starvation therapy is divided into three categories: enhanced single-starvation therapy, combination chemotherapy and enhanced O_2 supplement; oxidation therapy is also divided into three categories: enhanced single-oxidative therapy, facilitate the enzymatic process, and combination PDT/SDT/CDT.

follow (Fig. 1).

2.1. GOx-based nanocarriers enhanced starvation therapy

In recent years, cancer starvation therapy has emerged as an alternative strategy to preventing tumor growth by cutting the energy supply with few adverse effects. According to the Warburg effect, tumor cells require more glucose than normal tissue cells do. As a result, tumor growth will be preferentially stopped if glucose is scarce [21]. Numerous functional nanomaterials have been designed for enhancing tumor starvation treatment [22–24]. Vesicles are the most extensively utilized cellular transport vehicle, therefore encapsulating GOx within vesicles would be a preferable solution [25]. To illustrate the effectiveness of starvation therapy with vesicle-based delivery of GOx at the tumor site, Dinda and colleagues [26] observed that GOx-based starvation therapy with self-assembled vesicles was around 6-fold more effective against cancer cells (HeLa) than normal cells (NIH 3T3). However, given the tumor's heterogeneity and continuous blood supply, eradicating the tumor with a single starvation therapy is difficult.

When combined with chemotherapy, starvation therapy's ineffectiveness is considerably decreased. In this regard, Huang et al. [27] successfully augmented starvation-combined chemotherapy by delivering GOx and doxorubicin (DOX) using zeolite imidazole framework (ZIF)-based nanoparticles. Meanwhile, nanocarriers disintegrated and released Zn^{2+} into tumors, disabling mitochondria and damaging tumor cells' antioxidant systems, which boosted cancer starvation-combined chemotherapy. Furthermore, Zhang et al. [28] used AuNPs to co-load GOx and DOX, which can kill 80% of cancer cells when combined with 0.2 μg/mL of DOX and 22.5 pM of the nano-conjugate, demonstrating that the specific damage induced by the nano-conjugate can make cancer cells much more vulnerable to chemotherapy. Zhang and coworkers [29] put forward a multitherapy modality: tumor starvation triggered synergism with sensitized chemotherapy, integrating the characteristics of each therapy modality and material chemistry. Following the GOx starvation-induced amplification of pathological defects in tumors, chemotherapy is scheduled to be locally activated and accurately strengthened to provide the best possible multitherapy synergism from a spatial and temporal perspective. In response to hypoxia-induced by TME and GOx-mediated starvation therapy, hypoxia-activated prodrugs could effectively enhance GOx-based starvation therapy. Zhang and colleagues [30] proposed a novel technique for delivering GOx and hypoxia-activated prodrugs tirapazamine (TPZ) via liposomal nanocarriers by combining starvation therapy with hypoxia-activated therapy, a synergistic therapeutic modality that improves the growth inhibitory effect of 4T1 tumors. Similarly, Mei et al. [31] exploited TME-mediated cascaded nanoreactor to achieve the perfect combination of self-enhanced catalytic therapy and hypoxia activated TPZ chemotherapy.

Although hypoxia undermines the efficiency of GOx-based starvation therapy, MnO_2 and Catalase (CAT) can catalyze the breakdown of H_2O_2 into oxygen, relieving hypoxia in starvation therapy. Kou et al. designed FePt/MnO_2/GOx-based synergistic therapy in which the accumulation of gluconic acid and H_2O_2 from glucose consumption promotes MnO_2 catalytic efficiency, resulting in the sustained generation of O_2 [32]. Similar to this, Zhou et al. [33] created a therapeutic strategy for augmenting starvation therapy with oxygen self-supply using metal-organic framework MOF-embedded GOx and CAT. By catalyzing the decomposition of H_2O_2 generated by GOx to produce additional oxygen, CAT can amplify the effectiveness of O_2-dependent starvation therapy.

2.2. GOx-based nanocarriers enhanced oxidative therapy

Oxidative therapy is a novel approach to cancer treatment that involves specifically enhancing oxidative stress in cancer cells above the toxicity threshold [34]. Reactive oxygen species (ROS) [35], the basis of oxidative therapy, is a broad term for a class of tiny, chemically active molecules containing oxygen, which includes superoxide radicals (O_2^-), nitric oxide (NO), and hydroxyl radicals (•OH), as well as non-radicals like H_2O_2 and singlet oxygen ($^1O_2$). GOx consumes glucose while boosting H_2O_2 production. High H_2O_2 accumulation caused by GOx oxidation of glucose has an effect on killing cancer cells via ROS activation. Zhao and colleagues [36] designed a glucose-responsive GOx-polymer nanogel for synergistic melanoma starvation and oxidative therapy by regulating H_2O_2, mediated by GOx. More importantly, nanogels not only boosted GOx's anticancer efficacy, but also reduced GOx's side effects by restricting GOx to the tumor site.

In addition, to further enhance the efficacy of GOx-mediated oxidative therapy, enhancement of enzymatic processes is a possible pathway. For instance, Li and coworkers [37] developed GOx-loaded therapeutic polymeric nanoreactors (theraNRs) with a vesicle structure that were adopted to facilitate the enzymatic process for inducing oxidative stress locally in response to the TME. TheraNRs can induce oxidative stress not only by depleting glucose to produce H_2O_2 but also by reducing GSH-mediated ROS scavenging, resulting in cancer cell death and tumor elimination. Likewise, Wei al et [38].developed multienzyme nanoreactors based on iridium/ruthenium (IrRu) with cascade catalytic potential to treat breast cancer via synergistic oxidative and starvation therapy. IrRu catalyzed the conversion of glucose to H_2O_2, whereas GOx catalyzed the conversion of H_2O_2 to the lethal poisonous $^1O_2$ and O_2. Among them, $^1O_2$ might directly increase cancer cell apoptosis through oxidative treatment, and O_2 assisted in alleviating the hypoxia problem associated with starvation therapy.

To increase ROS cytotoxicity, oxidative therapies are used in conjunction with photodynamic therapy (PDT) [39], sonodynamic therapy (SDT) [40], and chemodynamic therapy (CDT) [41]. Compared to mild H_2O_2-induced oxidative therapy, PDT and SDT employed ROS produced following laser or ultrasound irradiation, respectively. Zhou and coworkers [33] proposed a strategy of cascade reaction-enhanced combined therapy based on the O_2-evolving multifunctional nanoreactors. Biomimetic mineralization was used to encapsulate GOx and CAT in an MOF to increase their stability through spatial confinement. Furthermore, H_2O_2 created by GOx can be broken down by CAT and continue to produce O_2, improving the efficacy of O_2-dependent starvation therapy and PDT. Furthermore, Zhou et al. [42] created PdPt bimetallic nanocatalysts in collaboration with GOx and the acoustic sensitizer IR780 for NIR-II photothermal enhanced tumor starvation and SDT, supplemented with an oxygen self-supply strategy. The combination of

starvation therapy and SDT in this nano-reactor results in complete tumor clearance. Simultaneously, it induces immunogenic cell death and boosts anti-tumor immunity. Given that nanotitania can generate a variety of ROS (such as $^1O_2$, OH, etc.) in response to ultrasound stimulation, Xue and colleagues [43] conceived and built a smart nanoplatform to immobilize GOx utilizing a TiO_2@Pt Schottky junction. TiO_2@Pt produced $^1O_2$ and hydroxyl radicals (•OH) more quickly when exposed to ultrasound, whereas Pt-catalyzed O_2 self-supply increased the buildup of ROS and GOx-mediated glucose depletion. The finding implied that TiO_2@Pt/GOx (TPG) mediated SDT and starvation therapy promote systemic tumor suppression while relieving hypoxia in the TME. Since 2016, Prof. Wenbo Bu has proposed CDT that activates nanomedicine Fenton-like processes to produce powerful •OH for tumor-specific therapy [44]. Iron-related nanoparticles are strongly related to the Fenton reaction, in which iron-based materials catalyze H_2O_2 to form O_2 and H_2O under neutral conditions but highly toxic •OH under acidic conditions. Hu et al. [45] created TPZ@FeMSN-GOx by synthesizing iron-doped mesoporous silica nanoparticles (FeMSNs) loaded with chemotherapeutic drug TPZ. More interesting, intracellular reduced GSH promotes Fe^{3+} to Fe^{2+} conversion, which eventually decomposes H_2O_2 to •OH, ensuring efficient CDT.

3. GOx-based nanocarriers for tumor target therapeutic applications

Considering the superior tumor-killing efficacy of GOx-based nanocarriers and their elucidated killing mechanism, additional effective techniques to increase delivery efficiency beyond 0.7% will be developed [46]. As shown in Fig. 2, passive targeting and active targeting were critical in tumor therapy. Given the unique advantages of active targeting, such as the effective enhancement of tumor cell endocytosis, we will focus on the application of GOx-based active targeting in tumor therapy.

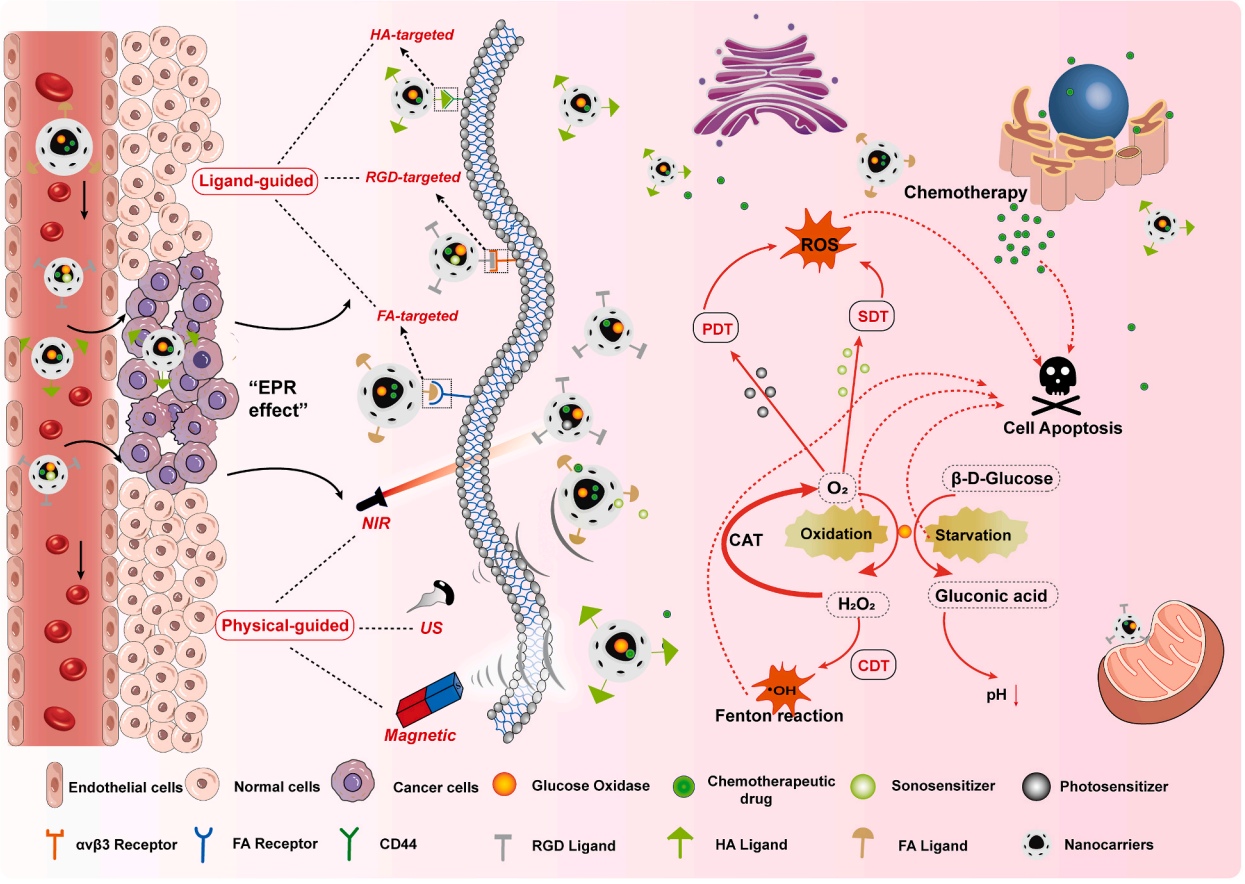

Fig. 2. Schematic Diagram GOx-based Nanocarriers for Tumor Targeting Therapy
Notes: Tumor-targeted therapies are typically divided into two types: passive targeting and active targeting. Passive targeting relies on tumor-specific EPR effects to promote drug aggregation in tumor tissues, whereas active targeting therapies are frequently mediated by ligands or physical modalities to effectively improve targeting. Given the unique starvation and oxidative therapies of GOx, the development of GOx-based nanoparticle drug delivery system dramatically improves the efficacy of tumor-targeted therapies and creates a solid foundation for clinical translation.

3.1. Passive targeting

The delivery of nanocarriers via the EPR effect is regarded as the most significant achievement in the field of targeted cancer medication therapy [47] (Fig. 2). Nanocarriers of around 100 nm in size are believed to exhibit a robust EPR effect. Maeda first proposed the EPR effect in 1986, noting that the majority of solid tumors had blood vessels with poor structure and increased vascular permeability to guarantee a sufficient supply of nutrition and oxygen to tumor tissues for rapid growth [30,31]. Passive targeting is summarized in Table 1.

Ren et al. [49] invented a self-assembled bioreactor cascade (FeS-GOx nanodots) to improve nanocarrier penetration and tumor treatment efficacy. The larger FeS-GOx@PTX (FGP) was generated by co-assembling FeS-GOx nanodots and hydrophobically introducing the chemotherapeutic drug paclitaxel (PTX). The larger FGP nanodots could effectively accumulate in the tumor after intravenous injection due to the EPR effect. In addition, Bao et al. [50] employed erythrocyte membrane (EM) coated nanocarriers to increase SDT efficacy and in vivo compatibility. Furthermore, the PCN-224@Pt@GOx@EM nanocarriers preferentially aggregate in tumor tissues via the EPR effect and kill tumor cells by local ROS generation via US irradiation. The passive targeting ability of nanocarriers has been effectively utilized to enhance drug accumulation in cancerous tissue while minimizing adverse effects. The EPR effect allows nano-drugs to passively aggregate at tumor sites; nevertheless, the anticancer effects of this effect are limited. Modulation of tumor vasculature is thought to be a viable method for increasing EPR efficiency [59]. Nitric oxide (NO), as an endogenous gas transmitter, is frequently utilized to relax blood arteries, improve circulation, and boost oxygen supply. Deepagan et al. [60] prepared nitric oxide-producing nanoparticles (NO-NPs) for site-specific delivery of NO to tumor sites and showed that NO-NPs increased blood flow by approximately 30% compared to the control group, in addition to the increased vascular permeability observed after treatment by in vitro imaging. NO-NPs enhanced the EPR effect and reduced tumor development without causing considerable damage to normal tissues. Given that the EPR impact is only significant in mouse models, more reliable methods of boosting the EPR effect in human tumors and improving treatment efficacy are required.

Table 1
GOx-based passively targeted nanocarriers for tumour therapy.

Nanocarrier style	Basic Materials	Diameters (nm)	Half-time	Reach Maximum Accumulation Time	Biosafety evaluation	Tumor Treated	Refs
MTO-GOx@γ-Fe_2O_3 NPs	Fe_2O_3 NPs	154.7 nm	N.A.	6 h	No obvious hemolysis; No body wight loss; Safe for major organs	Breast cancer	[48]
FeS-GOx@PTX NPs	Nanodots	160 nm	N.A.	24 h	No distinct tissue damage; Safe for the liver and kidney	Breast cancer	[49]
PCN-224@Pt@GOx@EM nanocarriers	MOF	121.8 ± 3.4 nm	4.21 ± 0.17 h	24 h	Safe for major organs; No obvious function damage and pathological alteration	Pancreatic cancer	[50]
GOx-Pt-NS	Pt-NP	N.A.	N.A.	N.A.	No hepatorenal toxicity	Cancercolon	[51]
CuS-PGH NMs	PLL	N.A.	N.A.	6 h	Safe for major organs	Breast cancer	[52]
GOx-MnCaP NPs	MnCaP	131 ± 26 nm	N.A.	N.A.	Hemolysis below 2.26%; No body weight loss; Safe for the liver and kidney	Breast cancer	[53]
GMCD	MnCaP	138 ± 36 nm	48 h	24 h	No obvious hemolysis; No body weightloss; Safe for major organs	Breast cancer	[54]
PGC-DOX	CuCaP	88 ± 17 nm	24 h	12 h	Hemolysis below 3.0%; No body weight loss; Safe for major organs	Breast cancer	[55]
GOx-based NPs	SRF/tPy-Cy/PTX	178.4 nm	N.A.	24 h	No significant acute toxicity; No obvious hemolysis	Breast cancer	[56]
pGUnTG65	glycopolymer	145 nm	2.814 ± 1.104 h	4 h	No blood biochemical abnormalities; Safe for major organs	Breast cancer	[57]
PMNSG	PdMo bimetallene nanosheet	56 nm	N.A.	4 h	No pathological abnormality or inflammation; No abnormalities in blood biochemistry	Breast cancer	[58]

Abbreviations: PTX: paclitaxel; GOx: glucose oxidase; MTO: mitoxantrone; Pt: platinum; EM: Erythrocyte membrane; MOF: metal-organic framework; NM: nanomedicine; PLL: poly(L-lysine); GMCD: catalase and sinoporphyrin sodium in the manganese(Mn)-doped calcium phosphate mineralized glucose oxidase nanoparticles; PGC-DOX: poly(ethylene glycol) (PEG)-modified glucose oxidase (GOx) as a template to form biodegradable copper-doped calcium phosphate (CuCaP) NPs; SRF: sorafenib; PTX: paclitaxel; PMNSG: PdMo bimetallene nanosheet + Glucose oxidase.

Table 2
Summary of GOx-based active targeting nanocarriers for delivering anti-cancer drugs.

Ligands/ Exogenous stimuli	Nanocarrier styles	Target spot	Half-time	Reach Maximum Accumulation Time	Biosafety evaluation	Tumor Treated	Refs
RGD-guided	Met/GOx@His/ZIF-8~RGD	$\alpha_v\beta_3$ integrin	2.63 h	4 h	No body wight loss; Safe for the liver and kidney; No blood biochemistry abnormalities.	Breast cancer	[63]
	RGD-mGZD	$\alpha_v\beta_3$ integrin	N.A.	24 h	No body wight loss; Safe for the major organs; No blood biochemistry abnormalities.	Cervix cancer Glioblastoma	[64]
	ICGOx@IO-Dox-EGCG-PPP	$\alpha_v\beta_3$ integrin	N.A.	N.A.	No effect on heart	Melanoma	[65]
	AuNP-PEG-RGD-GOx plus Dox	$\alpha_v\beta_3$ integrin	N.A.	24 h	N.A.	Breast cancer	[28]
HA-guided	Cur@MOF-GOx/HA	CD44 receptor	N.A.	N.A.	No body wight loss; Safe for the liver and kidney; Hemolysis below 5%;	Breast cancer	[66]
	Fe_3O_4@MON/MnO_2@HA-GOD/Sor	CD44 receptor	N.A.	N.A.	No body wight loss; Safe for the major organs;	Liver cancer	[67]
	Pd@Pt-GOx/HA	CD44 receptor	N.A.	12 h	Safe for the major organs; No blood biochemistry abnormalities.	Breast cancer	[68]
	IrO_2-GOx@HA NPs	CD44 receptor	N.A.	6 h	No body wight loss; Safe for the major organs;	Breast cancer	[69]
	DOX&GGF@ZIF-8@HA	CD44 receptor	N.A.	48 h	No body wight loss; Safe for the major organs;	Breast cancer	[70]
	FC-BBR/IND@GOD@HA NPs	CD44 receptor	N.A.	N.A.	N.A.	Liver cancer	[71]
	HG-MIL@PDA NPs	CD44 receptor	4.84 h	24 h	No body wight loss; Safe for the major organs;	Breast cancer	[72]
	PTFCG@MH	CD44 receptor	N.A.	1 h	No body wight loss; Safe for the major organs;	Breast cancer	[73]
	PBMO-GH	CD44 receptor	3.11 h	6 h	No body wight loss; Safe for the major organs; Hemolysis below 4.12%;	Breast cancer	[74]
	Cu-MOF/GOD@HA	CD44 receptor	N.A.	N.A.	Hemolysis below 4%	Breast cancer	[75]
	PTX/MnO_2/GOx-Lip-HAs	CD44 receptor	N.A.	N.A.	Safe for the major organs; No blood biochemistry abnormalities.	Cervical cancer	[76]
	MSNs-GOx/PLL/HA	CD44 receptor	N.A.	N.A.	No body wight loss; Safe for the major organs;	Breast cancer Liver cancer	[77]
	AS/GOD@HA ZnO NPs	CD44 receptor	N.A.	N.A.	No body wight loss; Safe for the major organs;	Breast cancer	[78]
	MPG-HA Nanoparticles	CD44 receptor	N.A.	N.A.	Safe for the major organs	Breast cancer	[79]
FA-guided	MnO_2-PDA-FA	folate receptor	N.A.	N.A.	N.A.	Liver cancer	[80]
	FeHF-GOx/CAT	folate receptor	N.A.	N.A.	No body wight loss;	Breast cancer	[81]
	Hb-PDA-Fe@GOD@PEG-FA	folate receptor	N.A.	24 h	No blood biochemistry abnormalities.	Cervical cancer Melanoma	[82]
	AR6-DOX-GOx@PDA-FA-Siram	folate receptor	N.A.	N.A.	N.A.	Liver cancer	[83]

(*continued on next page*)

Table 2 (*continued*)

Ligands/ Exogenous stimuli	Nanocarrier styles	Target spot	Half-time	Reach Maximum Accumulation Time	Biosafety evaluation	Tumor Treated	Refs
AS1411 aptamers	Gel-GOx-Fc	nucleolin	N.A.	N.A.	N.A.	Cervical cancer Breast cancer	[84]
anti-LILRB4 Antibody	FTG/L&SMD	LILRB4	N.A.	N.A.	Safe for the major organs; Hemolysis below 4%;	Lung cancer	[85]
TrF	IGTCDs	Transferrin receptor	N.A.	N.A.	Safe for the major organs;	Gliomas	[86]
light-guided	Ce6/GOx@ZIF-8/ PDA@MnO2	cancer-targeting NIR	N.A.	N.A.	Safe for the major organs;	Breast cancer	[87]
	CPPO@porphyrin-MOF@Cancer cell membrane GOD	cancer-targeting NIR	N.A.	N.A.	Safe for the major organs;	Breast cancer	[88]
	COF@GOx&CAT	cancer-targeting NIR	N.A.	N.A.	No body wight loss; Safe for the major organs; No blood biochemistry abnormalities.	Breast cancer	[89]
	GOx/CAT-NC	cancer-targeting NIR	N.A.	N.A.	N.A.	Breast cancer	[90]
	GOx-MSN@MnPc-LP	cancer-targeting NIR	N.A.	N.A.	No body wight loss; Safe for the major organs;	Breast cancer	[91]
	γ-PGA@GOx@Mn,Cu-CDs NPs.	cancer-targeting NIR	N.A.	36 h	No body wight loss; Safe for the major organs;	Breast cancer	[92]
	MONs-GOx@MnO_2–Ce6	cancer-targeting NIR	N.A.	4 h	No body wight loss; Safe for the major organs;	Cervical cancer	[93]
	CPCG	cancer-targeting NIR	N.A.	4 h	No body wight loss; Safe for the major organs;	Cervical cancer	[94]
	HMSNs-GOx-Ce6@CPPO-PFC/O_2@C	cancer-targeting NIR	N.A.	N.A.	N.A.	Melanoma	[95]
ultrasound-guided	PdPt@GOx/IR780	cancer-targeting US	N.A.	N.A.	No body wight loss; Safe for the major organs; Hemolysis only 2%	Breast cancer	[42]
	GOD/CAT@ZPF-Lips	cancer-targeting US	N.A.	N.A.	N.A.	Breast cancer	[96]
	GOx-MnO_2/HMME	cancer-targeting US	N.A.	N.A.	N.A.	Breast cancer	[97]
	TiO_2@Pt/GOx	cancer-targeting US	N.A.	24 h	No body wight loss; Safe for the major organs;	Breast cancer	[43]
magnetic-guided	GOx@PLGA-Fe_3O_4	cancer-targeting Magnetic	N.A.	N.A.	No body wight loss; Safe for the major organs; No blood biochemistry abnormalities.	Breast cancer	[98]
	GOD-PTL-Lips@MNPs	cancer-targeting Magnetic	N.A.	N.A.	N.A.	Cervical cancer	[99]
	HIONCs-GOD	cancer-targeting Magnetic	N.A.	N.A.	N.A.	Prostate cancer	[100]
	pLFePt-GOx	cancer-targeting Magnetic	4.2 h	N.A.	No body wight loss; Safe for the major organs;	Breast cancer	[101]

Abbreviations: Met: metformin; ZIF: histidine; His: zeolitic imidazolate framework-8; RGD-mGZD: composed of RBCm, DSPE-PEG2000-RGD peptide, ZIF-8, GOx and DOX; ICG: indocyanine green; IO: iron oxide; EGCG: Epigallocatechin-3-gallate; Cur: curcumin; MOF: metal–organic frameworks; GOx: glucose oxidase; GOD: glucose oxidase; PEG: Polyethylene glycol; IrO2: iridium dioxide; Cur: curcumin; AS: Artesunate; HA: hyaluronic acid; Sor: Sorafenib; MON: mesoporous organosilica nanoparticles; GGF: GOx and GA/Fe nanocomplexes; BBR: Berberine; PDA: polydopamine; HG: HA and GOx; MIL: metal–organic frameworks (MOFs) based on iron(III) carboxylate material; Ce6: chlorin e6; MnO2: manganese dioxide; PB:

prussian blue; MSNs: mesoporous silica nanoparticle; Fc: ferrocene; TRF: transferrin; MIONzyme: iron oxide-based nanozymes; COF: porphyrin-based covalent organic framework; CAT: catalase; MnPc: manganese phthaleincyanide; LP: Liposome; γ-PGA: polymer-poly (γ-glutamic acid); CD: carbon dots; CPCG: polyethylene glycol (PEG) functionalized cerium oxide nanoparticles (CeO_2) with photosensitizer chlorin e6 (Ce6) and glucose oxidase (GOx); HMSNs: hollow mesoporous silica nanoparticles; CPPO:bis[2,4,5-trichloro-6-(pentyloxycarbonyl)phenyl] oxalate PFC: perfluorohexane; ZPF: the frameworks of zeolitic pyrimidine; HMME: hematoporphyrin monomethyl ether; PLGA: poly(lactic-*co*-glycolic acid); PTL: parthenolide.

3.2. Active targeting

Even though tumor-targeting capabilities might be passively improved by nanotechnology-based drug delivery via the EPR effect, accumulating evidence suggests that drug penetration and accumulation in tumor tissues still need to be improved [61]. Active targeting nanocarriers can be designed based on two different targeting mechanisms, ligand-directed targeting [62] and physical-directed targeting of the tumor cells (Fig. 2). Ligand-directed active targeting is presented in terms of tumor-penetrating peptides arginine-glycine-aspartic acid (RGD), hyaluronic acid (HA), and folate (FA), while physically-directed active targeting focuses on the application of exogenous laser, ultrasound, and magnetic fields (Table 2).

3.2.1. GOx-based ligand-instructed active tumor targeting therapy

Active targeting nanomaterials are often modified by tumor penetration peptides (RGD), HA, FA, or other tumor marker ligands, conferring specific targeting ability while lowering non-specific targeting. In view of the variety of ligand modifications, we will use representative RGD, HA, and FA ligands as examples.

3.2.1.1. RGD. The RGD peptide is a tumor-homing and tissue-penetrating peptide that binds to $\alpha_v\beta_3$ integrins and then enzymatically forms CRGDK/R, which interacts with neuropilin-1 to enhance medicine tissue penetration and tumor targeting [102]. The RGD peptide is currently gaining interest as a promising delivery moiety for enhancing chemotherapeutic agent intra-tumoral penetration via angiogenetic arteries [103]. Covalent conjugation and co-administration with anti-cancer chemicals or drug delivery vehicles are two ways RGD technology can be used to improve chemotherapeutic efficacy [104]. Given the importance of anaerobic glycolysis in tumor cell proliferation [105], treating tumors by disrupting their metabolic pathways has evolved into a sophisticated strategy. Some related work has been reported. For example, Meng et al. [63] developed smart nanodrugs for cancer synergistic therapy that are based on glucose depletion and glycolysis suppression. Met and GOx were encapsulated in His/ZIF-8 and coated with RGD peptide for enhanced targeting to obtain the desired nanodrug (Met/GOx@His/ZIF-8), and based on in vitro and in vivo experiments, the combination of glycolysis inhibition and starvation therapy compared with Met- or GOx-mediated monotherapy showed efficient cancer cell growth inhibition and superior antitumor properties. Using an RGD-targeting peptide, Ke et al. [64] constructed a multifunctional MOF nanoparticle with erythrocyte membrane modification for co-starvation chemotherapy. The addition of the erythrocyte membrane increases blood circulation time, while the RGD peptide alteration allows for preferential targeting of the tumor site. The TME increased GOx starvation therapy and caused the structural collapse of MOF, causing DOX release and thereby enhancing chemotherapy, according to the findings. In addition, Wu et al. [106] created biodegradable nanocatalysts to accomplish targeted/synergistic cancer nanodrugs and controlled CO release by altering the TME. To exclusively target $\alpha_v\beta_3$ integrin overexpressing cancer cells, the nanocatalysts combined GOD and H_2O_2-sensitive manganese carbonyl (MnCO) encased hollow mesoporous organosilicon nanoparticles (HMONs), along with RGD for surface modification. By combining gas therapy and starvation therapy, the nanocatalysts achieved excellent efficacy at the cellular level as well as in animal tumor xenograft models. Although GOx-based therapy coupled with chemotherapy can suppress tumor growth, antineoplastic medication efficacy will be hampered if multi-drug resistance (MDR) arises. Zhang et al. [28] created a nanocouple (AuNP-PEG-RGD-GOx) that specifically targets cancer cells with RGD-targeting peptide, which interferes with cancer cells' metabolic disorder by exhausting intracellular glucose and O_2, thereby raising cancer cell sensitivity to chemotherapy. Meanwhile, H_2O_2 and gluconic acid synthesis causes apoptosis in chemotherapy-sensitive cancer cells. This combinatorial therapeutic technique significantly slows the evolution of MDR and reactivates drug-sensitive MDR breast cancer cells. Despite encouraging evidence in the literature, significant challenges remain, such as non-specific adhesion since RGD receptors are found in both benign and pathological tissues.

3.2.1.2. HA. Hyaluronic acid (HA) is a naturally occurring acid mucopolysaccharide found in synovial fluid and the extracellular matrix [107]. Due to its excellent biocompatibility, HA has been widely used in tissue engineering, drug delivery, and molecular imaging [108,109]. HA-modified inorganic nanocarriers for GOx and antitumor drug co-delivery have been shown in studies to have a wide range of applications. Since endogenous GSH scavenges •OH and insufficient intracellular H_2O_2 limit CDT efficacy, Li et al. [76] introduced a high-efficiency nanodrug delivery method (PTX/MnO_2/GOx-Lip-HAs) for improving tumor targeting and CDT efficacy. The addition of HA increased the targeting of nanocarriers and displayed effective tumor suppression with few side effects. Similarly, Ren and colleagues [78] created HA-functionalized ZnO NPs that co-delivered Artesunate (AS) and GOD. The affinity of HA and CD44 receptors boosted the active targeting of ZnO NPs, whereas ZnO NPs released loaded AS and GOD in acidic TME while generating excess ROS generation, resulting in tumor cell destruction. This combination of ROS-based oxidative damage and starvation therapy resulted in superior cancer treatment outcomes. Fu et al. [110] used a biomineralization technique to create a tumor-targeting and TME-activated calcium phosphate ($CaPO_4$) nanotherapeutic system based on GOx and loaded with L-arginine (L-Arg) and modified HA to achieve active selectivity for CD44 overexpressed cancer cells. A strong synergistic therapeutic effect was observed in 4T1 tumor-bearing mice via the cascade interaction of GOx and L-Arg, with no major toxic side effects. A unique multifunctional nanoreactor Pd@PtGOx/HA was effectively created by Ming et al. [68] to address the low efficacy of GOx-mediated starvation therapy as

well as any potential adverse effects on healthy tissues. The treatment efficacy and biosafety are significantly increased while it can target CD44 overexpressing cancer cells with intracellular Hyase-responsive GOx, CAT-like and peroxidase (POD)-like activities and GSH oxidation capabilities. Furthermore, GOx synergized with Pd@Pt to deplete intratumoral glucose and create •OH to provide starvation-enhanced CDT for efficient cancer therapy.

3.2.1.3. FA. Folate (FA) [111] is an essential B vitamin for DNA replication and cell division. Most cancer cells contain higher quantities of folate receptors on their surfaces; thus, the folate receptor can be a therapeutic target for tumors. Given that high GSH and hypoxic circumstances restrict the efficacy of GOx-mediated starvation therapy, Song et al. [80] developed a porous clad spherical structure and modified it with polydopamine (PDA) and FA, while loading GOx and CPT Foremore, enzyme-laden nanosystems with multimodal therapeutic activities are becoming increasingly popular in the treatment of cancer, and Wen et al. [81] devised and manufactured a cascade of dual enzyme-enhanced Fe-hemoporfin framework nanosensitizers for synergistic acoustodynamic-starvation tumor treatment. The PEGylated FA modification successfully prolonged the cycling cycle of enzyme-carrying nanosystems and improved their targeting, while FeHF-GOx/CAT enhanced the therapeutic efficiency of SDT. Similar to this, Yuan et al. [82] prepared nano-modulators using simple self-assembly between polymers (PDA and PEG-FA), catalysts (Fe), and proteins (Hb and GOD), which consists of hemoglobin (Hb) and ferric ion (Fe^{3+}) co-conjugated PDA as core, GOD as shell, and FA modified polyethylene glycol (PEG) as the corona. The results of in vitro and in vivo tests revealed that tumor-bearing mice had good tumor suppression and high survival rates after nanomodulator administration. The binding of FA to folate receptors improves tumor cell endocytosis, and when combined with other medications, the therapy is improved. However, the ligand receptor's mechanism of action, which must be examined in terms of affinity, will favor the future development of FA-mediated active targeting.

3.2.1.4. Others. In addition to specific ligands playing a vital role in active tumor targeting treatment, there are other interesting findings to investigate the tumor targeting therapy. Targeting mitochondria to disrupt redox homeostasis has become a hot topic in tumor therapy. For co-starvation and PDT, Luo et al. [112] used a composite enzyme nanogel composed of the mitochondrial target triphenylphosphine (TPP), GOx and CAT, and protoporphyrin IX (PpIX). The nanogel successfully boosted the stability of natural enzymes and improved the catalytic efficiency of the cascade. TPP can also precisely target the mitochondria of 4T1 cells, thereby damaging the mitochondria of cancer cells and triggering tumor cell death. As a nanomaterial, carbon dots have been studied and applied in many aspects, Liu et al. [86] used a hydrothermal technique to create iron-doped orange carbon dots (ICDs) and then combined the transferrin (TRF) and GOD to create IGTCDs with targeting, therapeutic, and imaging activities. The multifunctional nanocatalysts accelerated the enzymatic generation of H_2O_2 from glucose, triggering the release of ROS for effective glioma targeting and killing.

3.2.2. GOx-based physical-instructed active tumor targeting therapy

Ligand-directed active targeting employs ligand-receptor binding to modulate the response ligand on the surface of the nanocarrier; however, physically guided active targeting uses an applied light, ultrasound, and magnetic field to guide tumor targeting.

Photodynamic targeting therapy, also known as photodynamic therapy (PDT), is a method of treating disease with photodynamic action in which a photosensitizer and O_2 are involved in causing functional or morphological changes in the organism's cells or biomolecules under the action of light, leading to cellular damage. PDT typically relies on the cytotoxic $^1O_2$ generated when a photosensitizer transfers energy from its active state to the adjacent O_2 in the light radiation environment, killing cancer cells. Due to their non-invasiveness, light-specific toxicity, and temporal-spatial controllability, PDT has been widely employed in preclinical and clinical studies. Due to TME containing abundant H_2O_2, MnO_2 nanostructures or peroxidase can be utilized to promote H_2O_2 decomposition and in situ O_2 generation. Thus, cancer starvation therapy and PDT can be enhanced by combining GOx and H_2O_2 administration. Liu and colleagues [73] created self-assembled nanoparticles coated with GOx and Ce6 for PDT to reverse multi-drug resistance using poly (D, L-lactic-*co*-glycolic acid) (PLGA), MOF, and MnO_2. GOx catalyzed glucose degradation to inhibit ATP generation, and the resulting H_2O_2 was catalyzed by MnO_2 to produce oxygen, alleviating tumor hypoxia and sensitizing the PDT, and the GSH was also consumed by MnO_2 to inhibit the tumor's antioxidant system, resulting in an effective tumor inhibition. Given the high stability and satisfactory biocompatibility of nanogels [113], Luo et al. [112] prepared a mitochondria-targeting complex enzyme nanogel loaded with GOx and CAT by a simple synthetic method, which catalytically enhances PDT to generate ROS through cycling and destroys mitochondria in cancer cells, leading to apoptosis. Due to the catalytic characteristics of iridium dioxide, IrO_2 nanoparticles (IrO_2 NPs) were created by Yuan and colleagues [69] via a simple method that possesses excellent photothermal/photodynamic effects as well as peroxidase-like activity. The in situ amplifier produced at the TME by the combination of GOx and IrO_2 NPs improved the type II impact of PDT while also exacerbating apoptosis in breast cancer (4T1) cells. PDT is a promising therapy option for superficial tumors or lesions, but it is ineffective against deep cancer metastasis sites due to light penetration.

Sonodynamic therapy is based on the formation of cytotoxic ROS from the sonosensitizer via ultrasound-triggered cavitation. SDT, in terms of non-invasive treatment, is more promising than photo-inspired therapy because of deeper tissue penetration, high precision, fewer side effects, and low cost [114]. Moreover, nanoparticle-based ultrasound sensitizers provide important benefits such as enhanced efficacy, binding activity, and target specificity of SDT due to the simplicity of design afforded by nanotechnology [115]. SDT is expected to solve the treatment depth and reactive oxygen toxicity of PDT due to the combination of ultrasound and acoustic sensitizer. Studies have shown that there are three main mechanisms of action of SDT [115,116], ultrasonic cavitation effects, free radical and $^1O_2$ production, and US-induced direct cancer cell apoptosis are all examples. Up until now, organic and inorganic nanoparticles are the two major types of acoustic sensitizers that activate SDT [117]. Organic usually have disadvantages such as poor

hydrophobicity, low bioavailability, rapid elimination, and insufficient tumor accumulation. In contrast, due to their excellent ultrasonic stability, tumor selectivity, and extended blood circulation, inorganic acoustic sensitizers [118] (TiO_2) have a strong potential for SDT applications. For instance, Zhao et al. [43] created a TiO_2@Pt/GOx smart nanoplatform by immobilizing the surface of the GOx onto TiO_2@Pt. It promoted systemic tumor suppression after hypoxia relief in the TME using SDT and starvation therapy. However, before inorganic sensitizers may be employed in the clinic, the issue of unclear biodegradation must be solved. This could explain why organic chemicals with enhanced biodegradability and biocompatibility are now considered more feasible cancer SDT alternatives. To further boost SDT efficiency, Bao et al. [50] developed an erythrocyte membrane-encapsulated MOF consisting of porphyrinic PCN-224 NPs integrated with platinum (Pt) and GOx. Additionally, the tumor absorbs the nanocarriers, which increases the SDT action by Pt catalyzing the generation of O_2 from H_2O_2 on their surface to relieve tumor hypoxia. Zhang et al. [97] developed a cascade catalytic nanoplatform coated with acoustic sensitiser (haematoporphyrin monomethyl ether, HMME) and GOx based on MnO_2 NPs. Due to the H_2O_2 catalysis of MnO_2, the oxygen-dependent challenges of starvation therapy and SDT were solved. Similarly, Wen et al. [81] constructed a dual enzyme (GOx and CAT) nanosystem, which is more efficient in glucose consumption and more efficient in ultrasound-triggered $^1O_2$ production.

A magnetic targeting drug delivery system (MTDDS) is a system that directs the motion and concentration of drug-loaded nanomaterials in vivo using an applied magnetic field [119]. Monitoring the magnetic field strength in vitro and targeting drug delivery can raise drug concentration near the target site, decrease drug dosage, and minimize adverse effects on other normal body tissues. The •OH can be directly created by various metal ion-mediated Fenton or Fenton-like processes to break down H_2O_2 in the tumor site [120]. Up to now, several works have been published in this regard. For instance, Zhang et al. constructed an autocatalytic Fenton nanosystem by encapsulating GOx in ZIF and then coating the obtained NPs with a metal polyphenol network [121]. Feng and colleagues [122] developed magnetically targeted and TME-responsive nanocatalysts with high enzyme loading and manganese dioxide (MnO_2) nanoshells to avoid early GOD leakage. After entering the tumor cells by magnetic targeting, the anti-cancer efficacy is boosted by the acidic microenvironment created by GOD starvation therapy and the enormous amount of H_2O_2 created to stimulate the subsequent Fenton reaction. Facing the same problem, Chen et al. [123] developed a tumor-targeted and TME-responsive nanoreactor containing iron tetroxide nanoparticles (Fe_3O_4 NPs) and GOD, The one-piece nanoreactor achieved a progressive process of tumor accumulation, physiological response, glucose depletion and hydroxyl radical production, effectively inhibiting tumor growth. Given the likelihood that MRI will play a significant role in correcting the Fenton catalyst's low efficiency and the lack of H_2O_2 expression in cells, Zhou et al. [98] successfully manufactured magnetic nanoparticles for dual-modal imaging (MRI and photoacoustic imaging) to guide Fenton-like reactions in tumor areas. Further, Zhang et al. [101] used magnetic resonance imaging (MRI) guidance to create a PDGFB-targeted, biodegradable FePt alloy assembly for chemotherapy and starvation-enhanced CDT. ROS-mediated apoptosis and iron death, as well as glucose depletion-mediated starvation therapy, yielded excellent anticancer action once again. Magnetic targeting in combination with chemotherapy has demonstrated excellent therapeutic efficacy, Chi et al. [67] constructed multiresponsive multifunctional magnetic NPs loaded with Sorafenib (Sor), in which Fe_3O_4 magnetic NPs are coated with mesoporous organosilicon nanoparticles (MON) to form a "core-shell" structure. GOD catalyzes the synthesis of H_2O_2 from glucose as well as the Fenton reaction with iron ions to produce •OH, resulting in a potent tumor-killing impact.

4. Conclusions and future perspective

Due to its outstanding β-D-glucose catalytic efficiency, GOx has recently attracted the interest of researchers in the field of cancer treatment. GOx catalyzes the conversion of glucose to hydrogen peroxide and gluconic acid while also using oxygen. GOx depletes oxygen for tumor starvation treatment while producing H_2O_2 for oxidative therapy. However, starvation and oxidative therapies are also controversial. With the advancement of nanotechnology [81], nanocarrier systems have alleviated some of the problems encountered by GOx, and so nanocarriers have evolved to target tumors using GOx as a carrier.

The mechanism of GOx-based nanocarriers killing effect on tumor cells, and active-passive targeting therapy, which includes ligand-modified and exogenous stimulus-responsive active targeting therapy, are all carefully discussed in this review (laser, ultrasound and magnetic field). Additionally, it also emphasizes the critical significance of GOx synergistic therapy and encourages more and better research on targeted nanomaterials for tumor applications. Although considerable progress has been achieved with GOx-based nano-targeted tumor therapy, it is still in its early phases, and there is still a long way to go from basic investigations to clinical translation, as well as some important challenges to overcome.

First, glucose and oxygen serve as substrates for glucose oxidase throughout the body, and GOx-catalyzed glucose generation of H_2O_2 may threaten systemic toxicity [82]. Previous studies have shown that intra-tumoral injection followed by additional antioxidant supplementation reduces GOx systemic toxicity, as does GOx covalently bound to polystyrene microspheres to prolong H_2O_2 production at the site of delivery. Previous studies have shown that intratumoral injection of antioxidants and covalent binding of GOx to polystyrene microspheres are effective in reducing the systemic toxicity of GOx. Although GOx oxidizes glucose to produce H_2O_2 and gluconic acid, both of which can be employed in starvation and oxidative therapy, GOx is an oxygen-demanding enzyme, and its catalytic activity is susceptible to the tumor's hypoxic milieu of the tumor, limiting its utility. As a result, some studies are being conducted into the role of GOx while autonomously producing oxygen to continually supply GOx for catalysis, creating a positive cycle that can address GOx inadequacies. To further the therapeutic effect, Wang et al. built a multifunctional therapeutic integrated nanoplatform (MG@PNPs), while GOx locally consumed glucose to produce tumor cell starvation. The production of O_2 by MG @ PNPs can help to increase the effectiveness of oxygen-dependent SDT and starvation therapy [112]. To improve tumor hypoxia and enhance the efficiency of GOx catalytic reaction, the Huang group [21] created a unique self-oxygenation/hyperthermia-promoted tumor starvation therapy by building an MNS-GOx nanodrug delivery system with both photothermal and catalytic H_2O_2 breakdown, which

may accomplish TME response degradation as well as photoacoustic/magnetic resonance (MRI) dual-modality imaging capability to track the treatment process. Similar to this, Zhao et al. [108] created TiO_2@Pt/GOx with success, which then enabled starvation therapy and SDT to support systemic tumor suppression while reducing hypoxia in the TME. The effectiveness of starvation therapy was significantly increased by this self-supply of oxygen catalyzed by Pt, and it also provided a logical plan for GOx-based combination therapy.

Second, a wide variety of complex therapeutic nanocarriers have been used to include GOx for synergistic tumor therapy. Nanoparticle surface modifications are mostly employed to improve blood circulation time as well as tumor targeting capabilities. Their sophisticated manufacture and vulnerability to immune system hazards, however, make them difficult to replicate and restrict their progress from the bench to the bedside. Studies have shown that microfluidic and non-wetting template (PRINT) technologies enable high-speed self-assembly of NPs with narrower size distributions, tunable physical and chemical properties, and improved batch-to-batch reproducibility. As a result, PRINT and microfluidics technologies can meet the demand for industrial-scale nanocarrier synthesis, which can speed up clinical translation.

Third, before approaching the clinic, the long-term biosafety of GOx nanodrugs must be thoroughly examined by systematic research. Most GOx-based nanocarriers are non-biodegradable, cannot be eliminated efficiently by the kidneys, and pose a high risk of systemic toxicity. Thus, degradable nanocarriers should be considered due to the safety of nanocarriers in vivo. The primary focus of current preclinical studies on the efficacy of nanomedicines is proof-of-concept; however, in-depth in vivo research, including long-term safety, cannot be exaggerated. A study team [86] created a nano-drug GOx-MnCaP-DOX with both biodegradability and acid responsiveness of the TME, which was employed to accomplish efficient synergistic treatment of tumor MRI tracing. Meanwhile, the material breakdown products Ca^{2+} and PO_4^{3-} can participate in normal human metabolism; hence, the material has good biosafety and potential clinical *trans*-application value. Furthermore, to generate more therapeutically relevant in vivo data, numerous in vivo investigations of human xenograft tumor models have been frequently used. We hypothesize that patient-derived xenograft tumors developed from genetically modified or humanized mouse-like animals may perform better than cultured cancer cell lines obtained from immunodeficient mice. Furthermore, the introduction of artificial intelligence (AI) approaches may be a promising solution to long-term biosafety issues, since AI is capable of optimizing nanomaterial synthesis as well as fast screening and exploring the interactions of nanomaterials with physiological tissues via simulation experiments [124]. Based on this, we believe that we can consider generating an open database that can analyze the efficiency of nanoparticle tumor delivery and safety evaluation in real-time.

Fourth, there has been a minor improvement in the selection of active targeting ligands and receptors. Monoclonal antibodies are employed in targeted therapy because they have excellent selectivity and binding affinity for the target receptor. Its in vivo application, however, is exceedingly immunogenic, whereas the antibody fragments scFv and Fab are substantially less immunogenic and thus preferable for active targeting. Likewise, aptamers with comparable non-immunogenic properties have been chemically improved for in vivo application. Transferrin and folic acid have been used as targeting ligands to target transferrin receptors and folate receptors, which are overexpressed not just on tumor cells, but also on metastatic and drug-resistant malignant cells. There is currently no established best targeting strategy; each has its advantages and disadvantages. Perhaps a combination of tactics can be used to improve drug delivery precision, paving the path for more successful tailored therapy. In addition, the focus should be on utilizing basic research to design the optimal nanocarriers for targeting and testing them in a variety of animal models in the future, not limited to mice, which could be geared toward mechanistic studies while determining delivery efficiencies and laying the groundwork for clinical translation.

Fifth, analyzing the effect of the nanomaterials themselves and their medicines on clinical translation is critical. First, a crucial stage in clinical translation is the evaluation of the safety of medications and nanomaterials. Second, we should pay attention to the stability and release rate of the drug; while nanocarriers play more of a transport role than the actual therapeutic one, the drug itself still plays the primary therapeutic role. This will help to further ensure the stability of the drug transport process and improve the release rate of intracellular release, which will help to accelerate the clinical translation; Third, we should prioritize both enhancing targeting and minimizing costs. Without a doubt, the choice of ligand and its ability to bind will have a substantial impact on targeting efficiency. Excellent nanomaterials combined with specific ligands can significantly improve targeting, however, boosting precise targeting will unavoidably increase the economic cost. From the point of clinical translation, the relationship between the two must be properly balanced; fourth, actual clinical needs and practicality must be examined. Fourth, clinical feasibility should be a key consideration. Clinical translation of nano drug delivery systems also requires clinical trials to assess their safety and efficacy in humans to determine their true clinical feasibility. In conclusion, careful consideration of their effects on stability, drug release, targeting, and safety should guide the choice of nanocarrier materials and the careful inclusion of supplementary pharmaceuticals. Strict preclinical testing, attention to regulatory requirements, and consideration of scalability and cost-effectiveness for practical implementation in healthcare settings are all necessary for successful clinical translation.

Funding

This research work was funded by the Grant Qinghai Provincial Natural Science Foundation Project (2022-ZJ-912).

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 71 (2021) 209–249.
[2] L. Zhang, W. Chen, S. Liu, C. Chen, Targeting breast cancer stem cells, Int. J. Biol. Sci. 19 (2023) 552–570.
[3] T.R. Cox, The matrix in cancer, Nat. Rev. Cancer 21 (2021) 217–238.
[4] J.N. Hennigan, M.D. Lynch, The past, present, and future of enzyme-based therapies, Drug Discov. Today 27 (2022) 117–133.
[5] M. Vellard, The enzyme as drug: application of enzymes as pharmaceuticals, Curr. Opin. Biotechnol. 14 (2003) 444–450.
[6] C.M. Haskell, G.P. Canellos, B.G. Leventhal, P.P. Carbone, J.B. Block, A.A. Serpick, O.S. Selawry, L-asparaginase, Therapeutic and toxic effects in patients with neoplastic disease, N. Engl. J. Med. 281 (1969) 1028–1034.
[7] L. Feun, N. Savaraj, Pegylated arginine deiminase: a novel anticancer enzyme agent, Expet Opin. Invest. Drugs 15 (2006) 815–822.
[8] L.H. Fu, C. Qi, J. Lin, P. Huang, Catalytic chemistry of glucose oxidase in cancer diagnosis and treatment, Chem. Soc. Rev. 47 (2018) 6454–6472.
[9] C.H. Wang, J.X. Yang, C.Y. Dong, S. Shi, Glucose oxidase-related cancer therapies, Adv. Ther. 3 (2020) 1–29.
[10] Z. Cheng, M. Li, R. Dey, Y. Chen, Nanomaterials for cancer therapy: current progress and perspectives, J. Hematol. Oncol. 14 (2021) 85–101.
[11] Y. Shi, R. van der Meel, X. Chen, T. Lammers, The EPR effect and beyond: strategies to improve tumor targeting and cancer nanomedicine treatment efficacy, Theranostics 10 (2020) 7921–7924.
[12] H.K. Patra, A.P.F. Turner, The potential legacy of cancer nanotechnology: cellular selection, Trends Biotechnol. 32 (2014) 21–31.
[13] M. Wang, D. Wang, Q. Chen, C. Li, Z. Li, J. Lin, Recent advances in glucose-oxidase-based nanocomposites for tumor therapy, Small 15 (2019), e1903895.
[14] L.H. Fu, C. Qi, J. Lin, P. Huang, Catalytic chemistry of glucose oxidase in cancer diagnosis and treatment, Chem. Soc. Rev. 47 (2018) 6454–6472.
[15] M. Coluccia, V. Parisse, P. Guglielmi, G. Giannini, D. Secci, Metal-organic frameworks (MOFs) as biomolecules drug delivery systems for anticancer purposes, Eur. J. Med. Chem. 244 (2022) 1–26.
[16] L.H. Fu, C. Qi, Y.R. Hu, J. Lin, P. Huang, Glucose oxidase-instructed multimodal synergistic cancer therapy, Adv Mater 31 (2019), e1808325.
[17] W. Cao, M. Jin, K. Yang, B. Chen, M. Xiong, X. Li, G. Cao, Fenton/Fenton-like metal-based nanomaterials combine with oxidase for synergistic tumor therapy, J Nanobiotechnology 19 (2021) 325–360.
[18] L.K. Boroughs, R.J. DeBerardinis, Metabolic pathways promoting cancer cell survival and growth, Nat. Cell Biol. 17 (2015) 351–359.
[19] J. Li, D. Tong, J. Lin, Current status of cancer starvation therapy, Zhejiang Da Xue Xue Bao Yi Xue Ban 51 (2022) 241–250.
[20] C. Lennicke, J. Rahn, R. Lichtenfels, L.A. Wessjohann, B. Seliger, Hydrogen peroxide- production, fate and role in redox signaling of tumor cells, Cell Commun. Signal. 13 (2015) 39–57.
[21] N.C. Denko, Hypoxia, HIF1 and glucose metabolism in the solid tumour, Nat. Rev. Cancer 8 (2008) 705–713.
[22] J. Yu, Z. Wei, Q. Li, F. Wan, Z. Chao, X. Zhang, L. Lin, H. Meng, L. Tian, Advanced cancer starvation therapy by simultaneous deprivation of lactate and glucose using a MOF nanoplatform, Adv. Sci. 8 (2021), e2101467.
[23] S. Yu, Z. Chen, X. Zeng, X. Chen, Z. Gu, Advances in nanomedicine for cancer starvation therapy, Theranostics 9 (2019) 8026–8047.
[24] M. Wang, M. Chang, P. Zheng, Q. Sun, G. Wang, J. Lin, C. Li, A noble AuPtAg-GOx nanozyme for synergistic tumor immunotherapy induced by starvation therapy-augmented mild photothermal therapy, Adv. Sci. 9 (2022), e2202332.
[25] W.C. Huang, W.-H. Chiang, Y.H. Cheng, W.C. Lin, C.F. Yu, C.Y. Yen, C.K. Yeh, C.S. Chern, C.S. Chiang, H.C. Chiu, Tumortropic monocyte-mediated delivery of echogenic polymer bubbles and therapeutic vesicles for chemotherapy of tumor hypoxia, Biomaterials 71 (2015) 71–83.
[26] S. Dinda, S. Sarkar, P. Das, Glucose oxidase mediated targeted cancer-starving therapy by biotinylated self-assembled vesicles, Chem. Commun. 54 (2018) 9929–9932.
[27] T. Huo, L. Chen, H. Nie, W. Li, C. Lin, M. Akhtar, R. Huang, Mitochondrial dysfunction and antioxidation dyshomeostasis-enhanced tumor starvation synergistic chemotherapy achieved using a metal-organic framework-based nano-enzyme reactor, ACS Appl. Mater. Interfaces 14 (2022) 3675–3684.
[28] J. Zhang, L.J. Liang, Z.Y. Li, Y.T. Shen, X. Guan, J. Yue, L.L. Cong, W.Q. Xu, W. Shi, C.Y. Liang, S.P. Xu, Multi-functionalized Nano-conjugate for combating multidrug resistant breast Cancer via starvation-assisted chemotherapy, Mater. Sci. Eng., C 116 (2020) 1–17.
[29] M.K. Zhang, C.X. Li, S.B. Wang, T. Liu, X.L. Song, X.Q. Yang, J. Feng, X.Z. Zhang, Tumor starvation induced spatiotemporal control over chemotherapy for synergistic therapy, Small 14 (2018), e1803602.
[30] R. Zhang, L.Z. Feng, Z.L. Dong, L. Wang, C. Liang, J.W. Chen, Q.X. Ma, R. Zhang, Q. Chen, Y.C. Wang, Z. Liu, Glucose & oxygen exhausting liposomes for combined cancer starvation and hypoxia-activated therapy, Biomaterials 162 (2018) 123–131.
[31] L.Q. Mei, D.Q. Ma, Q. Gao, X. Zhang, W.H. Fu, X.H. Dong, G.M. Xing, W.Y. Yin, Z.J. Gu, Y.L. Zhao, Glucose-responsive cascaded nanocatalytic reactor with self-modulation of the tumor microenvironment for enhanced chemo-catalytic therapy, Mater. Horiz. 7 (2020) 1834–1844.
[32] Y.K. Kou, Z.C. Dai, P. Cui, Z.F. Hu, L. Tian, F.F. Zhang, H.Q. Duan, Q.Y. Xia, Q.Y. Liu, X.W. Zheng, A flowerlike FePt/MnO_2/GOx-based cascade nanoreactor with sustainable O_2 supply for synergistic starvation-chemodynamic anticancer therapy, J. Mater. Chem. B 9 (2021) 8480–8490.
[33] Y. Zhou, B. Niu, Y. Zhao, J. Fu, T. Wen, K. Liao, G. Quan, X. Pan, C. Wu, Multifunctional nanoreactors-integrated microneedles for cascade reaction-enhanced cancer therapy, J. Contr. Release 339 (2021) 335–349.
[34] B. Perillo, M. Di Donato, A. Pezone, E. Di Zazzo, P. Giovannelli, G. Galasso, G. Castoria, A. Migliaccio, ROS in cancer therapy: the bright side of the moon, Exp. Mol. Med. 52 (2020) 192–203.
[35] H. Sies, D.P. Jones, Reactive oxygen species (ROS) as pleiotropic physiological signalling agents, Nat. Rev. Mol. Cell Biol. 21 (2020) 363–383.
[36] W. Zhao, J. Hu, W. Gao, Glucose oxidase-polymer nanogels for synergistic cancer-starving and oxidation therapy, ACS Appl. Mater. Interfaces 9 (2017) 23528–23535.
[37] J. Li, A. Dirisala, Z. Ge, Y. Wang, W. Yin, W. Ke, K. Toh, J. Xie, Y. Matsumoto, Y. Anraku, K. Osada, K. Kataoka, Therapeutic vesicular nanoreactors with tumor-specific activation and self-destruction for synergistic tumor ablation, Angew Chem. Int. Ed. Engl. 56 (2017) 14025–14030.
[38] C.F. Wei, Y.A. Liu, X.F. Zhu, X. Chen, Y.H. Zhou, G.L. Yuan, Y.C. Gong, J. Liu, Iridium/ruthenium nanozyme reactors with cascade catalytic ability for synergistic oxidation therapy and starvation therapy in the treatment of breast cancer, Biomaterials 238 (2020) 1–36.
[39] D.E.J.G.J. Dolmans, D. Fukumura, R.K. Jain, Photodynamic therapy for cancer, Nat. Rev. Cancer 3 (2003) 380–387.
[40] A.P. McHale, J.F. Callan, N. Nomikou, C. Fowley, B. Callan, Sonodynamic therapy: concept, mechanism and application to cancer treatment, Adv. Exp. Med. Biol. 880 (2016) 429–450.
[41] Z. Tang, Y. Liu, M. He, W. Bu, Chemodynamic therapy: tumour microenvironment-mediated Fenton and fenton-like reactions, Angew Chem. Int. Ed. Engl. 58 (2019) 946–956.
[42] Z.H. Zhou, J.S. Huang, Z.Y. Zhang, L. Zhang, Y. Cao, Z.G. Xu, Y.J. Kang, P. Xue, Bimetallic PdPt-based nanocatalysts for Photothermal-Augmented tumor starvation and sonodynamic therapy in NIR-II biowindow assisted by an oxygen Self-Supply strategy, Chem Eng J 435 (2022) 1–13.
[43] Y. Zhao, J. Liu, M. He, Q. Dong, L. Zhang, Z. Xu, Y. Kang, P. Xue, Platinum-titania Schottky junction as nanosonosensitizer, glucose scavenger, and tumor microenvironment-modulator for promoted cancer treatment, ACS Nano 16 (2022) 12118–12133.
[44] C. Zhang, W. Bu, D. Ni, S. Zhang, Q. Li, Z. Yao, J. Zhang, H. Yao, Z. Wang, J. Shi, Synthesis of iron nanometallic glasses and their application in cancer therapy by a localized Fenton reaction, Angew Chem. Int. Ed. Engl. 55 (2016) 2101–2106.

[45] Y. Hu, S. Bai, X. Fan, F. Zhou, B. Chen, S. Tan, H. Xu, A. Pan, S. Liang, Y. He, Autocatalytic oncotherapy nanosystem with glucose depletion for the cascade amplification of hypoxia-activated chemotherapy and H_2O_2-dependent chemodynamic therapy, Biomater. Sci. 10 (2022) 2358–2369.
[46] S. Wilhelm, A.J. Tavares, Q. Dai, S. Ohta, J. Audet, H.F. Dvorak, W.C.W. Chan, Analysis of nanoparticle delivery to tumours, Nat. Rev. Mater. 1 (2016) 1–12.
[47] Y. Zhou, X. Gao, Y. Lu, R. Zhang, K. Lv, J. Gong, J. Feng, H. Zhang, A pH-responsive charge-convertible drug delivery nanocarrier for precise starvation and chemo synergistic oncotherapy, Chempluschem 88 (2022), e202200394.
[48] Z. Zhong, C. Liu, Y. Xu, W. Si, W. Wang, L. Zhong, Y. Zhao, X. Dong, γ-Fe_2O_3 loading mitoxantrone and glucose oxidase for pH-responsive chemo/chemodynamic/photothermal synergistic cancer therapy, Adv. Healthcare Mater. 11 (2022), e2102632.
[49] H. Ren, J.H. Yong, Q.Q. Yang, Z. Yang, Z.Y. Liu, Y. Xu, H. Wang, X. Jiang, W.J. Miao, X.M. Li, Self-assembled FeS-based cascade bioreactor with enhanced tumor penetration and synergistic treatments to trigger robust cancer immunotherapy, Acta Pharm. Sin. B 11 (2021) 3244–3261.
[50] Y.H. Bao, J.F. Chen, H.Q. Qiu, C. Zhang, P.T. Huang, Z.W. Mao, W.J. Tong, Erythrocyte membrane-camouflaged PCN-224 nanocarriers integrated with platinum nanoparticles and glucose oxidase for enhanced tumor sonodynamic therapy and synergistic starvation therapy, ACS Appl. Mater. Interfaces 13 (2021) 24532–24542.
[51] J. Yu, X.D. He, Z.G. Wang, S. Liu, D.Y. Hao, X.Y. Li, Y.B. Huang, Combination of starvation therapy and Pt-NP based chemotherapy for synergistic cancer treatment, J. Mater. Chem. B 9 (2021) 6406–6411.
[52] Q. Chen, Z. Zheng, X. He, S. Rong, Y. Qin, X. Peng, R. Zhang, A tumor-targeted theranostic nanomedicine with strong absorption in the NIR-II biowindow for image-guided multi-gradient therapy, J. Mater. Chem. B 8 (2020) 9492–9501.
[53] L.H. Fu, Y.R. Hu, C. Qi, T. He, S. Jiang, C. Jiang, J. He, J. Qu, J. Lin, P. Huang, Biodegradable manganese-doped calcium phosphate nanotheranostics for traceable cascade reaction-enhanced anti-tumor therapy, ACS Nano 13 (2019) 13985–13994.
[54] L. Fu, Y. Wan, C. Li, C. Qi, T. He, C. Yang, Y. Zhang, J. Lin, P. Huang, Biodegradable calcium phosphate nanotheranostics with tumor-specific activatable cascade catalytic reactions-augmented photodynamic therapy, Adv. Funct. Mater. 31 (2021) 1–11.
[55] L.H. Fu, Y. Wan, C. Qi, J. He, C. Li, C. Yang, H. Xu, J. Lin, P. Huang, Nanocatalytic theranostics with glutathione depletion and enhanced reactive oxygen species generation for efficient cancer therapy, Adv Mater 33 (2021), e2006892.
[56] Y. Xiao, P. Chen, S. Lei, F. Bai, L. Fu, J. Lin, P. Huang, Biocatalytic depletion of tumorigenic energy sources driven by cascade reactions for efficient antitumor therapy, Angew. Chem. Int. Ed. 61 (2022), e202204584.
[57] M. Li, X. Luo, S. Lei, Y. Liu, H. Guo, Y. Zhang, Y. Pan, K. Chen, J. Lin, P. Huang, Synchronous interventions of glucose and mitochondrial metabolisms for antitumor bioenergetic therapy, Adv Mater 35 (2023), 2301099.
[58] S. Lei, J. Zhang, N.T. Blum, M. Li, D.Y. Zhang, W.M. Yin, F. Zhao, J. Lin, P. Huang, In vivo three-dimensional multispectral photoacoustic imaging of dual enzyme-driven cyclic cascade reaction for tumor catalytic therapy, Nat. Commun. 13 (2022).
[59] D.W. Siemann, M.R. Horsman, Modulation of the tumor vasculature and oxygenation to improve therapy, Pharmacol. Ther. 153 (2015) 107–124.
[60] V.G. Deepagan, H. Ko, S. Kwon, N.V. Rao, S.K. Kim, W. Um, S. Lee, J. Min, J. Lee, K.Y. Choi, S. Shin, M. Suh, J.H. Park, Intracellularly activatable nanovasodilators to enhance passive cancer targeting regime, Nano Lett. 18 (2018) 2637–2644.
[61] R. Sun, J. Xiang, Q. Zhou, Y. Piao, J. Tang, S. Shao, Z. Zhou, Y.H. Bae, Y. Shen, The tumor EPR effect for cancer drug delivery: current status, limitations, and alternatives, Adv. Drug Deliv. Rev. 191 (2022) 1–12.
[62] C.J. Su, A. Murugan, J.M. Linton, A. Yeluri, J. Bois, H. Klumpe, M.A. Langley, Y.E. Antebi, M.B. Elowitz, Ligand-receptor promiscuity enables cellular addressing, Cell Syst 13 (2022) 408–425.
[63] X.Y. Meng, Z.X. Lu, Q.Y. Lv, Y.Q. Jiang, L.M. Zhang, Z.F. Wang, Tumor metabolism destruction via metformin-based glycolysis inhibition and glucose oxidase-mediated glucose deprivation for enhanced cancer therapy, Acta Biomater. 145 (2022) 222–234.
[64] R.F. Ke, X.Y. Zhen, H.S. Wang, L.H. Li, H.Y. Wang, S.C. Wang, X.Y. Xie, Surface functionalized biomimetic bioreactors enable the targeted starvation-chemotherapy to glioma, J. Colloid Interface Sci. 609 (2022) 307–319.
[65] Q.T.H. Shubhra, K. Guo, Y.X. Liu, M. Razzak, M.S. Manir, A. Alam, Dual targeting smart drug delivery system for multimodal synergistic combination cancer therapy with re duce d cardiotoxicity, Acta Biomater. 131 (2021) 493–507.
[66] H. Yao, X. Gong, M. Geng, S. Duan, P. Qiao, F. Sun, Z. Zhu, B. Du, Cascade nanozymes based on the "butterfly effect" for enhanced starvation therapy through the regulation of autophagy, Biomater. Sci. 10 (2022) 4008–4022.
[67] H. Chi, G. Zhu, Y.L. Yin, H. Diao, Z.C. Liu, S.B. Sun, Z.M. Guo, W.P. Xu, J.Q. Xu, C.H. Cui, X.J. Xing, K. Ma, Dual-Responsive multifunctional "core-shell"magnetic nanoparticles promoting Fenton reaction for tumor ferroptosis therapy, Inter J Pharm 622 (2022) 1–11.
[68] J. Ming, T.B. Zhu, W.H. Yang, Y.R. Shi, D.D. Huang, J.C. Li, S.J. Xiang, J.J. Wang, X.L. Chen, N.F. Zheng, Pd@Pt-GOx/HA as a novel enzymatic cascade nanoreactor for high-efficiency starving-enhanced chemodynamic cancer therapy, ACS Appl. Mater. Interfaces 12 (2020) 51249–51262.
[69] X.Y. Yuan, J.Q. Cen, X. Chen, Z. Jia, X.F. Zhu, Y.Q. Huang, G.L. Yuan, J. Liu, Iridium oxide nanoparticles mediated enhanced photodynamic therapy combined with photothermal therapy in the treatment of breast cancer, J. Colloid Interface Sci. 605 (2022) 851–862.
[70] X. Fu, Y.L. Zhang, G.R. Zhang, X.G. Li, S.L. Ni, J.W. Cui, Targeted delivery of Fenton reaction packages and drugs for cancer theranostics, Appl. Mater. Today 26 (2022) 1–11.
[71] Y. Cheng, Y.H. Ji, D.F. Ouyang, FC-BBR/IND-induced glucose oxidase nanodrugs for targeted combination therapy, Inter J Pharm 611 (2022) 1–14.
[72] H.S. Wu, D.H. Gu, S.J. Xia, F.H. Chen, C.Q. You, B.W. Sun, One-for-all intelligent core-shell nanoparticles for tumor-specific photothermal-chemodynamic synergistic therapy, Biomater. Sci. 9 (2021) 1020–1033.
[73] P. Liu, Y. Zhou, X. Shi, Y. Yuan, Y. Peng, S. Hua, Q. Luo, J. Ding, Y. Li, W. Zhou, A cyclic nano-reactor achieving enhanced photodynamic tumor therapy by reversing multiple resistances, J Nanobiotechnology 19 (2021) 149–162.
[74] D.H. Gu, Z.K. Liu, H.S. Wu, P.J. An, X. Zhi, Y.J. Yin, W. Liu, B.W. Sun, Dual catalytic cascaded nanoplatform for photo/chemodynamic/starvation synergistic therapy, Colloids Surf. B Biointerfaces 199 (2021) 1–11.
[75] Y.N. Hao, C.C. Qu, Y. Shu, J.H. Wang, W. Chen, Construction of novel nanocomposites (Cu-MOF/GOD@HA) for chemodynamic therapy, Nanomaterials 11 (2021) 1–12.
[76] X.W. Li, X.Y. Zhang, W.D. Zhang, L. Li, W.B. Gao, X.W. Zhang, D.W. Gao, Biocatalysis of MnO_2-mediated nanosystem for enhanced multimodal therapy and real-time tracking, ACS Sustain Chem Eng 8 (2020) 13206–13214.
[77] X. Du, T. Zhang, G. Ma, X. Gu, G. Wang, J. Li, Glucose-responsive mesoporous silica nanoparticles to generation of hydrogen peroxide for synergistic cancer starvation and chemistry therapy, Int. J. Nanomed. 14 (2019) 2233–2251.
[78] Z. Ren, X. Han, L. Wang, Y. Wang, Hyaluronic acid functionalized ZnO nanoparticles co-deliver AS and GOD for synergistic cancer starvation and oxidative damage, Sci. Rep. 12 (2022) 4574–4587.
[79] C. Hu, J. Wang, S. Liu, L. Cai, Y. Zhou, X. Liu, M. Wang, Z. Liu, M. Pang, Urchin-shaped metal organic/hydrogen-bonded framework nanocomposite as a multifunctional nanoreactor for catalysis-enhanced synergetic therapy, ACS Appl. Mater. Interfaces 13 (2021) 4825–4834.
[80] S.H. Song, J.Y. Peng, Y.T. Wu, C. Li, D.Y. Shen, G. Yang, J.F. Liu, P.W. Gong, Z. Liu, Biomimetic synthesis of a novel O_2-regeneration nanosystem for enhanced starvation/chemo-therapy, Nanotechnology 33 (2022) 1–37.
[81] M. Wen, J.Y. Shen, Z.J. Wang, H.H. Guo, P. Geng, N. Yu, M.Q. Li, H.J. Zhang, M.F. Zhu, Z.G. Chen, A cascaded enzyme-loaded Fe-hemoporfin framework for synergistic sonodynamic-starvation therapy of tumors, Nanoscale 13 (2021) 5910–5920.
[82] P.Y. Yuan, G. Dou, T. Liu, X.Y. Guo, Y.K. Bai, D.K. Chu, S.Y. Liu, X. Chen, Y. Jin, On-demand manipulation of tumorigenic microenvironments by nano-modulator for synergistic tumor therapy, Biomaterials 275 (2021) 1–10.
[83] J.N. Lu, F.Y. Liu, H.J. Li, Y.Q. Xu, S.G. Sun, Width-consistent mesoporous silica nanorods with a precisely controlled aspect ratio for lysosome dysfunctional synergistic chemotherapy/photothermal therapy/starvation therapy/oxidative therapy, ACS Appl. Mater. Interfaces 12 (2020) 24611–24622.
[84] W.L. Song, P. Song, Y.J. Sun, Z.H. Zhang, H. Zhou, X.R. Zhang, P. He, Self-assembly of multifunctional DNA nanohydrogels with tumor microenvironment-responsive cascade reactions for cooperative cancer therapy, ACS Biomater. Sci. Eng. 7 (2021) 5165–5174.

[85] G. Zhu, H. Chi, M.C. Liu, Y.L. Yin, H. Diao, Z.C. Liu, Z.M. Guo, W.P. Xu, J.Q. Xu, C.H. Cui, X.J. Xing, K. Ma, Multifunctional "ball-rod" Janus nanoparticles boosting Fenton reaction for ferroptosis therapy of non-small cell lung cancer, J. Colloid Interface Sci. 621 (2022) 12–23.
[86] S. Liu, Z. Zhong, C. Zhang, Y. Zhou, C. Fu, X. Xu, Targeted therapy for the treatment of gliomas with multifunctional orange emissive carbon dots, Nanoscale Adv. 4 (2022) 894–903.
[87] L. Zhang, Z. Yang, W.S. He, J.H. Ren, C.Y. Wong, One-pot synthesis of a self-reinforcing cascade bioreactor for combined photodynamic/chemodynamic/starvation therapy, J. Colloid Interface Sci. 599 (2021) 543–555.
[88] S.Y. Yin, W. Liu, J.F. Yang, J.S. Li, Synergistically enhanced multienzyme catalytic nanoconjugates for efficient cancer therapy, J. Mater. Chem. B 9 (2021) 5877–5886.
[89] X.Y. Wan, H.W. Zhang, W. Pan, N. Li, B. Tang, An enzyme nanopocket based on covalent organic frameworks for long-term starvation therapy and enhanced photodynamic therapy of cancer, Chem Commun 57 (2021) 5402–5405.
[90] S.D. Liu, T.F. Yan, J.X. Sun, F. Li, J.Y. Xu, H.C. Sun, S.J. Yu, J.Q. Liu, Biomimetic cascade polymer nanoreactors for starvation and photodynamic cancer therapy, Molecules 26 (2021) 1–10.
[91] Y. Zhu, H.D. Shi, T.W. Li, J.N. Yu, Z.X. Guo, J.J. Cheng, Y.Z. Liu, A dual functional nanoreactor for synergistic starvation and photodynamic therapy, ACS Appl. Mater. Interfaces 12 (2020) 18309–18318.
[92] M. Zhang, W.T. Wang, F. Wu, T. Zheng, J. Ashley, M. Mohammadniaei, Q.C. Zhang, M.Q. Wang, L. Li, J. Shen, Y. Sun, Biodegradable Poly(gamma-glutamic acid)@glucose oxidase@carbon dot nanoparticles for simultaneous multimodal imaging and synergetic cancer therapy, Biomaterials 252 (2020) 1–36.
[93] C.L. Yang, Y.Z. Liu, S. Su, N. Gao, J. Jing, X.L. Zhang, A multifunctional oxygen-producing MnO_2-based nanoplatform for tumor microenvironment-activated imaging and combination therapy in vitro, J. Mater. Chem. B 8 (2020) 9943–9950.
[94] X.H. Liu, J. Liu, S.Y. Chen, Y.X. Xie, Q.L. Fan, J.H. Zhou, J.C. Bao, T.X. Wei, Z.H. Dai, Dual-path modulation of hydrogen peroxide to ameliorate hypoxia for enhancing photodynamic/starvation synergistic therapy, J. Mater. Chem. B 8 (2020) 9933–9942.
[95] Z. Yu, P. Zhou, W. Pan, N. Li, B. Tang, A biomimetic nanoreactor for synergistic chemiexcited photodynamic therapy and starvation therapy against tumor metastasis, Nat. Commun. 9 (2018) 1–9.
[96] W.C. Wu, Y.Y. Pu, H. Lin, H.L. Yao, J.L. Shi, Starvation-sensitized and oxygenation-promoted tumor sonodynamic therapy by a cascade enzymatic approach, Research 2021 (2021) 1–17.
[97] Y.J. Zhang, H.L. Wang, X.D. Jia, S.Z. Du, Y.Y. Yin, X.J. Zhang, Cascade catalytic nanoplatform for enhanced starvation and sonodynamic therapy, J. Drug Target. 28 (2020) 195–203.
[98] W.C. Zhou, X.Y. Tang, J. Huang, J.X. Wang, J.W. Zhao, L. Zhang, Z.G. Wang, P. Li, R. Li, Dual-imaging magnetic nanocatalysis based on Fenton-like reaction for tumor therapy, J. Mater. Chem. B 10 (2022) 3462–3473.
[99] W.B. Gao, S.P. Wei, Z. Li, L. Li, X.W. Zhang, C.H. Li, D.W. Gao, Nano magnetic liposomes-encapsulated parthenolide and glucose oxidase for ultra-efficient synergistic antitumor therapy, Nanotechnology 31 (2020) 1–25.
[100] W.W. Ying, Y. Zhang, W. Gao, X.J. Cai, G. Wang, X.F. Wu, L. Chen, Z.Y. Meng, Y.Y. Zheng, B. Hu, X.F. Lin, Hollow magnetic nanocatalysts drive starvation-chemodynamic-hyperthermia synergistic therapy for tumor, ACS Nano 14 (2020) 9662–9674.
[101] C. Zhang, Z. Leng, Y. Wang, L. Ran, X. Qin, H. Xin, X. Xu, G. Zhang, Z. Xu, PDGFB targeting biodegradable FePt alloy assembly for MRI guided starvation-enhancing chemodynamic therapy of cancer, J. Nanobiotechnol. 20 (2022) 264–278.
[102] I. Van Hove, T.T. Hu, K. Beets, T. Van Bergen, I. Etienne, A.W. Stitt, E. Vermassen, J.H.M. Feyen, Targeting RGD-binding integrins as an integrative therapy for diabetic retinopathy and neovascular age-related macular degeneration, Prog. Retin. Eye Res. 85 (2021), 100966.
[103] A. Sheikh, S. Md, P. Kesharwani, RGD engineered dendrimer nanotherapeutic as an emerging targeted approach in cancer therapy, J. Contr. Release 340 (2021) 221–242.
[104] S. Kang, S. Lee, S. Park, iRGD peptide as a tumor-penetrating enhancer for tumor-targeted drug delivery, Polymers 12 (2020) 1906–1932.
[105] A. Shafaee, D.Z. Dastyar, J.P. Islamian, M. Hatamian, Inhibition of tumor energy pathways for targeted esophagus cancer therapy, Metabolism 64 (2015) 1193–1198.
[106] J.R. Wu, Z.Y. Meng, A.A. Exner, X.J. Cai, X. Xie, B. Hu, Y. Chen, Y.Y. Zheng, Biodegradable cascade nanocatalysts enable tumor-microenvironment remodeling for controllable CO release and targeted/synergistic cancer nanotherapy, Biomaterials 276 (2021) 1–13.
[107] F. Della Sala, A. Fabozzi, M. di Gennaro, S. Nuzzo, P. Makvandi, N. Solimando, M. Pagliuca, A. Borzacchiello, Advances in hyaluronic-acid-based (Nano) Devices for cancer therapy, Macromol. Biosci. 22 (2022), e2100304.
[108] J. Zhou, M. Li, Y. Hou, Z. Luo, Q. Chen, H. Cao, R. Huo, C. Xue, L. Sutrisno, L. Hao, Y. Cao, H. Ran, L. Lu, K. Li, K. Cai, Engineering of a nanosized biocatalyst for combined tumor starvation and low-temperature photothermal therapy, ACS Nano 12 (2018) 2858–2872.
[109] S.Z.F. Phua, G. Yang, W.Q. Lim, A. Verma, H. Chen, T. Thanabalu, Y. Zhao, Catalase-integrated hyaluronic acid as nanocarriers for enhanced photodynamic therapy in solid tumor, ACS Nano 13 (2019) 4742–4751.
[110] L.H. Fu, C.Y. Li, W.M. Yin, Y.R. Hu, T.W. Sun, Y.L. Wan, J. Lin, Z.M. Li, P. Huang, A versatile calcium phosphate nanogenerator for tumor microenvironment-activated cancer synergistic therapy, Adv. Healthcare Mater. 10 (2021) 1–9.
[111] C.P. Leamon, J.A. Reddy, Folate-targeted chemotherapy, Adv. Drug Deliv. Rev. 56 (2004) 1127–1141.
[112] Z. Luo, X. Fan, Y. Chen, X. Lai, Z. Li, Y.L. Wu, C. He, Mitochondria targeted composite enzyme nanogels for synergistic starvation and photodynamic therapy, Nanoscale 13 (2021) 17737–17745.
[113] X. Ma, S.J. Li, Y. Liu, T. Zhang, P. Xue, Y. Kang, Z.J. Sun, Z. Xu, Bioengineered nanogels for cancer immunotherapy, Chem. Soc. Rev. 51 (2022) 5136–5174.
[114] Y. Zhang, X. Zhang, H. Yang, L. Yu, Y. Xu, A. Sharma, P. Yin, X. Li, J.S. Kim, Y. Sun, Advanced biotechnology-assisted precise sonodynamic therapy, Chem. Soc. Rev. 50 (2021) 11227–11248.
[115] X. Pan, H. Wang, S. Wang, X. Sun, L. Wang, W. Wang, H. Shen, H. Liu, Sonodynamic therapy (SDT): a novel strategy for cancer nanotheranostics, Sci. China Life Sci. 61 (2018) 415–426.
[116] X. Qian, Y. Zheng, Y. Chen, Micro/nanoparticle-augmented sonodynamic therapy (SDT): breaking the depth shallow of photoactivation, Adv Mater 28 (2016) 8097–8129.
[117] S. Son, J.H. Kim, X. Wang, C. Zhang, S.A. Yoon, J. Shin, A. Sharma, M.H. Lee, L. Cheng, J. Wu, J.S. Kim, Multifunctional sonosensitizers in sonodynamic cancer therapy, Chem. Soc. Rev. 49 (2020) 3244–3261.
[118] M. Aksel, Ö. Kesmez, A. Yavaş, M.D. Bilgin, Titaniumdioxide mediated sonophotodynamic therapy against prostate cancer, J. Photochem. Photobiol., B 225 (2021) 1–8.
[119] C. Sun, J.S.H. Lee, M. Zhang, Magnetic nanoparticles in MR imaging and drug delivery, Adv. Drug Deliv. Rev. 60 (2008) 1252–1265.
[120] Z. Tang, P. Zhao, H. Wang, Y. Liu, W. Bu, Biomedicine meets Fenton chemistry, Chem Rev 121 (2021) 1981–2019.
[121] L. Zhang, S.S. Wan, C.X. Li, L. Xu, H. Cheng, X.Z. Zhang, An adenosine triphosphate-responsive autocatalytic Fenton nanoparticle for tumor ablation with self-supplied H_2O_2 and acceleration of Fe(III)/Fe(II) conversion, Nano Lett. 18 (2018) 7609–7618.
[122] L. Feng, R. Xie, C. Wang, S. Gai, F. He, D. Yang, P. Yang, J. Lin, Magnetic targeting, tumor microenvironment-responsive intelligent nanocatalysts for enhanced tumor ablation, ACS Nano 12 (2018) 11000–11012.
[123] L. Chen, L. Zhao, G. Hu, R. Jin, B. Cai, Y. Bai, X. Chen, Tumor-specific nanomedicine via sequential catalytic reactions for accurate tumor therapy, J. Mater. Chem. B 8 (2020) 6857–6865.
[124] J.R. Clegg, A.S. Irani, E.W. Ander, C.M. Ludolph, A.K. Venkataraman, J.X. Zhong, N.A. Peppas, Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications, Sci. Adv. 5 (2019) 1–16.